REMARKS

Claims 1-37 are pending in the subject application. Claims 23-37 have been withdrawn from consideration. New claims 38 and 39 are added. In the present Office Action, claims 1-22 stand rejected on the grounds of nonstatutory obviousness type double patenting and under 35 U.S.C. § 112, first paragraph. Applicant respectfully traverses the rejection.

Nonstatutory Obviousness Type Double Patenting

The Examiner rejected claims 1-5, 13-15 and 22 on the ground of nonstatutory obviousness type double patenting in view of either U.S. Patents No. 6,127,134 or 6,426,190 in combination with JP5322770-Machine English Translation. The Examiner has also rejected claims 6 and 16 on the ground of nonstatutory obviousness type double patenting in view of either U.S. Patents No. 6,127,134 or 6,426,190 in combination with JP5322770-Machine English Translation. The Examiner appears to rely also on Potter, Electrophoresis, 1990, Vol. 11, pages 415-419, but Potter is only mentioned in the discussion following the statement of rejection of claims 6 and 16 and not in the rejection statement itself. Claims 7-12 were rejected on the ground of nonstatutory obviousness type double patenting in view of either U.S. Patents No. 6,127,134 or 6,426,190 in combination with JP5322770-Machine English Translation and in further combination with Anderson et al., Clinical Chemistry, 1981, Vol. 27, No. 11, pages 1807-1820. Claims 17-21 were rejected on the ground of nonstatutory obviousness type double patenting in view of either U.S. Patents No. 6,127,134 or 6,426,190 in combination with JP5322770-Machine English Translation and further in view of the Potter, Electrophoresis reference and the Anderson Clinical Chemistry reference.

Applicant submits herewith Terminal Disclaimers to disclaim the portion of the term of the patent that issues from the subject application that would extend beyond the full term of each of U.S. Patents Nos. 6,127,134 and 6,426,190. With the submission of the Terminal Disclaimers, the grounds for the nonstatutory obviousness type double

patenting rejections should be moot. Withdrawal of the rejections on obviousness type double patenting grounds is respectfully requested.

35 U.S.C. §112, first paragraph

The Examiner rejected claims 1-22 under 35 U.S.C. §112, first paragraph for failing to satisfy the written description requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner stated further that only the combination of Cy3 and Cy5 dyes are set forth in the application and further that the claimed matched set of dyes described "merely by their functional characteristics ... reads on an infinite number of dye compositions that are not possessed by Applicant."

The Examiner rightfully points out that the inventor must demonstrate possession of the invention to satisfy the written description requirement. Applicants respectfully disagree with the Examiner's conclusion that the subject matter of the claims was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Section 2163 of the Manual of Patent Examining Procedure (MPEP) provides that an" applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. (citation omitted Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by ... describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." *See also, Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006); *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1999).

Applicants submit, and will discuss more fully below, that the specification describes the claimed invention by describing the claimed invention with all of its limitations with words, structures and formulas and by discussing the identifying characteristics of the matched set of dyes in sufficient detail to allow one skilled in the art at the time the application was filed to make a wide variety of matched sets of dyes meeting the claimed criteria.

Section 2163 of the MPEP states further that "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." Citing, *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976). Exceptions arise when "the claims require an essential feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." MPEP at 2100-174. Applicants submit that all features of the claims are adequately described and that those in the art were sufficiently skilled in chemical synthesis to select dyes and modify the selected dyes to give the dyes the properties recited in the claims.

Showing possession does not require an actual reduction to practice. *Pfaff v. Wells Electronics*, 525 U.S. 55, 66 (1998); *Falkner v. Inglis*, 448 F.3d 1357, 1366-67 (Fed. Cir. 2006). Generally, an adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics. *Pfaff*, 525 U.S. at 68. The key to any demonstration of possession is that whatever method is used must describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession. *See Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 966 (Fed. Cir. 2002). The MPEP cites *Enzo Biochem.* at page 2100-179 where it provides that an "applicant may also show than an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure or some combination of such characteristics."

Differences in the type of invention claimed require different levels of detail to be disclosed and "the descriptive text needed . . . varies with the nature and scope of the invention at issue, and with the scientific and technical knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357, 1359 (Fed. Cir. 2005).

The court in *In re Herschler*, 591 F.2d 693, 702 (CCPA 1979) stated that "it is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that the appellants invented processes including those limitations." If a person with ordinary skill in the art would look at the examples provided and recognize that the properties which make the specific examples patentable would also apply to make the genus patentable as well, the written description requirement can be satisfied. *See Bilstad v. Wakalopulos*, 386 F.3d 116, 1125 (Fed. Cir. 2004); *Enzo Biochem*, 323 F.3d at 966.

In *Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006), the contested invention was a new method of making a poxvirus vaccine by inactivating an essential gene and placing the virus in a complementarily modified cell. The application described the process as to vaccine vectors in general and then focused on the subgenus of herpes virus, for which it provided a detailed example. *Id.* at 1364. The Court of Appeals for the Federal Circuit held that the descriptions provided were adequate to support a claim for the poxvirus vaccine, another subgenus of vaccine vectors, because essential genes for poxvirus were well known in the art and a skilled person would be able to choose an essential gene based on publicly available references. *Id.* at 1366.

In *Regents of the University of California v. Eli Lilly*, the Court of Appeals for the Federal Circuit held that

> [i]n claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the

> species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

119 F.3d 1559, 1568 (Fed. Cir. 1997).

In *Union Oil v. Atlantic Richfield*, the court rejected the argument that the patent was invalid because it described claimed gasoline mixtures by their "desired characteristics" rather than in terms of molecular structures or lists of ingredients. 208 F.3d 989, 992 (Fed. Cir. 2000). The court stated that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed'." *Id.* at 997. The patent taught how to vary the properties of gasoline to reduce emissions in such a way that skilled refiners would recognize that the inventor possessed the claimed invention at the time of filing. *Id.*

In *Herschler*, the court found that the functional description of "physiologically active substances" could support a claim to all steroids generally when only corticosteroids – a specific example within the larger genus of steroids – had been specifically discussed in the application. 591 F.2d 693, 697-98 (CCPA 1979). The court stated that, "[o]ccasionally, a functional recitation of those known [chemical] compounds in the specification may be sufficient as that description." *Id.* at 702.

The Examiner's rejection stated that the matched dye combinations were "described merely by their functional characteristics." However, functional descriptions can be adequate to meet the written description requirement when they are coupled with a known or disclosed correlation between function and structure. *See Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 964 (Fed. Cir. 2002); *In re Herschler*, 591 F.2d 693, 702 (CCPA 1979); *In re Edwards*, 568 F.2d 1349, 1352 (CCPA 1978). The MPEP itself states, "[t]he written description requirement may be satisfied through disclosure of function and minimal structure when there is a well established correlation between structure and function." MPEP §2163(II)(A)(3)(a)(i)(C)(2).

The law regarding the written description requirement is thus very clear that the applicant is not limited to the specific working examples in the specification. The specific examples of Cy3 and Cy5 dyes are not the only dyes that will work. They are a representation of the method of the invention using one example of a matched set of dyes.

Luminescent dyes for use in labeling cells, proteins and other compositions were well known to those skilled in the art and commercially available in 1995 when the grandparent application from which the subject application claims priority was filed. The chemical structures of the dyes, their molecular weights and their absorption and emission spectra were available from the manufacturers and distributors of the dyes. Those skilled in the art, upon reading the specification of the subject application, can make dyes of differing spectra that will be closely matched in molecular weight. The net charge of dyes and the ionic and pH characteristics of the dyes can be easily ascertained from the manufacturer or easily ascertained by one skilled in the art.

Applicants submit herewith, as an example of the type of commercial literature available, pages obtained from a search on Google® for luminescent dyes. One well known long time source of such dyes is Sigma-Aldrich Co. On the sigmaaldrich.com website, lists of dyes and their properties are available. In addition, literature references are advertised. On the page attached hereto, "Conn's Biological Stains, A Handbook of Dyes, Stains and Fluorochromes for Use in Biology and Medicine", 10th ed. is advertised. While the text advertised is current, the general description indicates that it has been available for 75 years and that the prior version was available 25 years ago. The Table of Contents lists many types of dyes, but not, as the Examiner states, an infinite number. Another page from the sigmaaldrich website attached to this Response advertises a text concerning industrial dyes. Again, this text is likely a current volume, but the general description states that dyes represent one of the very mature and traditional sectors of the chemical industry. This indicates that those skilled in the art in 1995 certainly would have understood, upon reading the specification of the subject application, that the applicants had possession of the claimed invention. They would

have understood, again based on the teachings of the specification coupled with the level of skill in the art, how to select from among the known dyes and how to adapt new dyes as they are later developed, and how to modify and analyze the known and new dyes to achieve a matched set of dyes that meets the criteria set forth in the claims of the subject application. An example of a new type of luminescent dye that claims to rival the cyanine dyes is attached hereto. A page from a product catalogue for "Dy" dyes, showing a wide variety of molecular weights, and absorption and emission spectra for these dyes is provided. While these dyes were not commercially available in 1995, they do demonstrate that those skilled in the art can make dyes of differing spectra that will be closely matched in molecular weight. The net charge of the dyes and the ionic and pH characteristics of the dyes can be easily ascertained.

The types and characteristics of many luminescent and fluorescent dyes were well known in 1995 and the type of information shown in the attachments is similar in character to that available from other manufacturers. Applicant is not required to describe in detail every embodiment of the dyes that will work in the claimed method.

The specification of the subject application provides at paragraph 036, as follows.

> In the process of the present invention, the fluorescent dyes are covalently coupled to proteins, preferably via lysine residues of the proteins, but coupling may also be to sulfhydryl or carboxylic acid groups in the proteins. For modified proteins, the dyes may be coupled to the modifying groups; for example the dyes may be coupled to the sugar residue of glycoproteins following oxidation thereof to the aldehyde. Regulation of the pH of proteins to force attachment of labels at one amino acid residue to the exclusion of other amino acids is a well known technique, as set forth in R. Baker, Organic Chemistry of Biological Components, (Prentice Hall, pub. 1971).

The specification thus provides reference to a text for regulating pH in proteins. Protein chemistry was well within the skill of the art in 1995. The procedures

for covalently binding portions of proteins and peptides to the functional groups mentioned as well as others, was well known.

The specification of the subject application further provides,

> When lysine is the attachment site, the covalent linkage destroys the positive charge of the primary amine of the lysine. Because isoelectric focusing depends on charge, it is important to compensate for the charge loss. A basic residue should remain basic. Changing the pKa of one residue per protein by as much as 3 can be tolerated, provided the basicity or acidity of the modified residue, as the case may be, is not altered. Dyes like rhodamine and fluorescein are not suitable because of the difference in charge.

The specification thus gives details about controlling the charge upon linkage and specific information about the degree to which the pKa may be changed. Those skilled in the art would certainly recognize that the applicants had possession of the invention. Applicants also give guidance as to what will not work. Those skilled in the art could discern the characteristics of the types of dyes that will work and those that will not. Coupled with the teachings of the requirements for the matched set of dyes and the ability of those in the art to buy, modify or synthesize their own dyes, knowledge of the types of dyes that will not work is useful information, again demonstrating that the applicants had possession of the claimed invention.

The specification states at paragraph 041 further that

> Fluorescent dyes that can be used for glycoprotein labeling include those dyes having hydrazine derivatives such as hydrazides, semicarbazides and carbohydrazides or amine derivatives as reactive groups. In order to maintain the overall charge on the glycoprotein, suitable dyes are those that bear an overall neutral charge. An overall neutral charge can be obtained by the addition of suitably charged linkers to the dye molecule to produce the desired

> overall charge. Suitable dyes would include neutral cyanine derivatives, BODIPY derivatives or other fluorescent derivatives available as matched dye sets as described herein and possessing an overall neutral charge.

The specification also states at paragraph 044,

> In order to maintain the overall charge on the phosphoprotein, suitable fluorescent imidazole derivatives would bear an overall negative charge. This overall negative charge could be obtained by the addition of a suitably charged linker to the dye molecule. Examples of dyes that can be used include, cyanine dyes bearing an overall negative charge, squarate dye derivatives bearing an overall negative charge or other fluorescent derivatives bearing an overall negative charge and available as matched dye sets. Preferred carbodiimide molecules are water soluble molecules such as (1-ethyl-3- (3-dimethylaminopropyl)-carbodiimide hydrochloride) (EDC) and 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide iodide) (EAC).

Cyanines and BODIPY™ dyes are not new inventions. The patent application provides detailed description about the qualities of matched sets of dyes and what needs to be done to create them (equalize charge etc.). Additionally, the example (Cy3 and Cy5) provides an illustration of the general principles that could be applied to the creation of any matched set of dyes. Someone with ordinary skill in the art should be able to read the general description and understand that the detailed methods provided in the specific example could be applied to create matched sets of dyes from cyanines or from BODIPY™ dyes.

Moreover, the specification provides a very detailed description of cyanine dyes in general, including general structures, and instructions for modifying the linker groups and compensating for changes in molecular weight of the dye due to changes in the linker with comparable changes in other portions of the molecule. See paragraphs beginning at 045 and 047-048. U.S. Patent No. 5,627,027 to Waggoner which describes the cyanines dyes in

general is incorporated by reference. The '027 patent discloses a number of cyanine type dyes; not just Cy3 and Cy5 dyes. Methods for modifying the various cyanine type dyes are disclosed.

See also the teachings regarding compensating for the addition of linkers at paragraph 047.

> The difference in molecular weight caused by changing the linker length in the fluorescent cyanine dyes can be compensated for by modulating the size of an aliphatic chain R_1 or R_2, attached to one of the dye's indole rings. One of R_1 or R_2 must be a reactive group.

The specification is not limited to a description of the cyanine dyes. At paragraph 049, the specification provides details about another dye and provides as follows.

> The cyanine dyes are one choice for the matched set of dyes of the present invention. Other dye compounds may be used in place of the cyanines, such as dipyrromethene boron difluoride dyes, the derivatized 4,4-difluoro-4-bora-3a,4a,-diaza-S-indacene dyes, described in U.S. Patent No. 4,774,339 to Haugland et al. and incorporated herein by reference, which are sold by Molecular Probes, Inc. under the trademark BODIPY®. The BODIPY® dyes, which have no net charge, are covalently linked to lysine side chains using an activated n-hydroxysuccinimidyl ester which forms an amide bond. The result is the loss of the lysine positive charge. Therefore, a positively charged linker group is used in the matched dyes of the invention to replace the lost primary amine with the linker's tertiary amine. The procedures for making BODIPY® dyes are described in U.S. Patent No. 4,774,339. Addition of the positively charged linker is by techniques well known to those skilled in the art. A linker can be designed with three functional groups; (1) to react with the BODIPY®-NHS ester, (2) to carry the desired charge, and (3) to be activated so that the

BODIPY®-linker construct will react with specific amino acid residues of the proteins in the extract.

The specification incorporates by reference the patent literature describing how to make the BODIPY® dyes and where to purchase the dyes. The referenced '339 patent describes the absorption and emission spectra of the BODIPY® dyes. The specification also describes how to modify the BODIPY® dyes.

The specification also discusses at paragraph 050 the way in which the charge can be maintained in the dyes.

The major considerations for the matched set of dyes are the maintenance of charge and distinct and different spectral characteristics. Any neutral dyes with a positive linker or any positively charged dyes, preferably each having a +1 charge, that otherwise satisfy the requirements described herein can serve as the dyes in the matched set of dyes of the present invention. Roughly equal molecular weight in the samples of labeled protein is desirable, but as explained above, not critical. The intrinsic positive charge of cyanine dyes is advantageously used in the preferred embodiment to replace the positive charge of lysine. The pK_a of cyanines and lysine are rather different; however, conditions were selected for dye:protein ratio to be less than one. This low level of labeling ensures that there will be negligible changes in the protein's migration on two-dimensional electrophoresis gels. Dyes may be used which match the pK_a of lysine more closely. Alternately, dyes that modify other amino acid residues may be used, provided the amino acid's ionic characteristics are preserved by the modification. Instead of a lysine, the attachment site on the protein may be a sulfhydryl or carboxylic group. When a sulfhydryl group is the attachment site on the protein, the corresponding attachment site on the dye is an iodoalkyl or maleimide group. When a carboxylic acid group is the attachment site on the protein, the corresponding attachment site on the dye is a chloroketone or a carbodiimide.

The disclosure is sufficiently detailed and includes such relevant identifying characteristics of the matched set of dyes to provide evidence that applicants were in possession of the claimed invention. The specification describes the claimed invention by means of words, general and specific structures, reference to texts, scientific literature and issued patents, specific working examples of a representative matched set of dyes and instructions for achieving the modifications necessary to control the ionic and pH characteristics and molecular weights of the dyes chosen which have the desired absorption and emission spectra.

Applicants submit that the written description requirement of the first paragraph of section 112 is fully satisfied. Withdrawal of the rejection under section 112 is respectfully requested.

New Claims

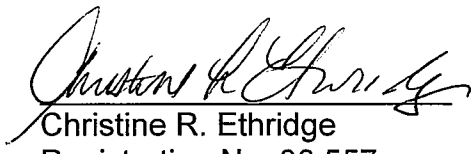
Applicants submit herewith new claims 38-39 which add limitations regarding the types of dyes from which the matched set of dyes can be selected. Consideration and allowance of claims 38-39 are respectfully requested.

CONCLUSION

Applicants submit that claims 1-22 and new claims 38-39 of the subject application are described in sufficient detail to allow those skilled in the art at the time the application was filed to know that applicants had possession of the full scope of the invention as claimed. Given the commercial availability of many dyes, and the information about the molecular weight and charge of the dyes that the manufacturers provide, the patent and non patent literature available about the chemistry of dyes and the chemistry of proteins and peptides and the level of skill in the art, applicants have provided more than enough information to allow those skilled in the art to conclude that applicants were in possession of the generic matched set of dyes recited in the claimed invention. Applicants submit that claims 1-22 and 38-39 are in condition for allowance. Accordingly, reconsideration and allowance of all pending claims are earnestly solicited. If the Examiner agrees that a generic claim is allowable, consideration and allowance of the withdrawn species claims 23-32 are respectfully requested.

If the undersigned can be of assistance to the Examiner in addressing issues to advance the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,



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